question the necessity of this threshold. In fact, moderate control in this study was independently associated with lower mortality and major complications among patients after isolated coronary revascularization. On the basis of our findings, we believe that moderate glycemic control (150 mg/dL ± 15%) may be superior to tight control (≤126 mg/dL) and entails few hypoglycemic events. Further randomized prospective studies evaluating the optimal postoperative glycemic regimen are necessary.

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Discussion

Dr Anthony P. Furnary *(Portland, Ore).* Dr Ailawadi, since I have to make this short, I really can't make it sweet. I thought your title was very clever, but the simple statistical fact is that neither the title nor the conclusions are supported in any way by the data presented, nor is it possible that any difference between tight

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and moderate control, if it did actually exist, could have ever been statistically detected in this study.

Let me explain. There are 134 patients in the tight group and 2700 in the moderate group. Because of the lack of a sufficient number of patients in the tight group, the study was markedly underpowered to detect any differences between the tight and moderate groups. Power analysis reveals that the estimated power of this study to detect a 1% absolute reduction in mortality between these 2 groups was only 3%, nowhere near the 80% power sought to ensure a valid finding. A quick χ^2 analysis comparing your mortality data between these 2 groups shows a *P* value of .6. Even if there had been no deaths at all in the tight group, the *P* value would have still been insignificant at .1.

Furthermore, your study is based entirely on retrospective data abstracted from an administrative—read ''billing''—database. Not a clinical database, not an STS database, an administrative database. Clinical outcomes from these databases are ''assumed'' by interpreting coding information that is applied to patient charts by hospital coders after discharge. Then, rather than using established STS predicted risk scores, which you had, for logistic risk adjustment, a new regression model was created.

What you have shown is that moderate control is superior to no control at all, and this is a finding that is supported by 15 years of published literature on the subject. Moderate control reduced mortality by 40% relative to no control. Interestingly, the point estimate for tight control shows a 50% reduction in mortality relative to the no control group. Again, however, there weren't enough patients to bring that point estimate to statistical significance; even had there been no deaths at all in the tight control group, it wouldn't have made it into the equation. To take those results and imply that moderate control is superior to tight control when they weren't even directly compared, simply because it didn't make it into the equation because of the low number of patients, is either wishful thinking or misleading marketing rhetoric that is not supported by your statistical data.

I have similar concerns about your morbidity statistics and conclusions. I don't have time to go into them here. In addition, however, of the 5 major complications that you have analyzed, 3 of them—stroke, prolonged ventilation, and reoperation—have never ever been shown to be associated with, let alone caused by, hyperglycemia in cardiac surgical patients. Thus the treatment studied, glycemic control, is unrelated to the complications examined. It would be like looking at the effect of antibiotics on atrial fibrillation rate.

We all know our first responsibility is to our patients, and we all come to this meeting looking for a sound bite, something we can take home, something that we can implement in our practice. It just worries me that the conclusion that you present, that moderate control is ''superior'' to tight control, is a dangerous message to let out, because the simple fact is that it is not supported by your data.

I have 3 questions. First, you cite moderate control articles from the medical ICU literature that don't include patients undergoing CABG. Why should we as cardiac surgeons ignore both randomized and observational cardiac-specific trials totaling more than 36,000 patients that tell us that the optimal target for patients undergoing CABG is in the range of 80 to 130 mg/dL in deference to your 134 mg/dL tight glycemic control patients?

Dr Ailawadi. Thank you for your comments. Getting back to the comment about our use of a clinical data repository, these data were merged with our STS database. We did use our STS data, not purely administrative data. We actually merged the data sets. So we believe that this actually provides better data and more complete data, because the STS, as you know, does not include many of these things that we are examining.

With the comment about stroke having never been associated with glucose strategy, there was a randomized trial of 400 patients by Gandhi published a couple of years ago comparing tight glucose control with a more liberal or a more moderate glucose control, similarly to our study. It was a randomized study, and they did find a worse stroke rate in patients with tight control. I realize that it is not a perfect study, but that has been shown before.

In terms of the question about medical intensive care unit, if you actually look at the NICE-SUGAR trial, although the article does not specify the number of patients who underwent cardiac surgery, it did include both medical and surgical patients. If you actually look, some of the centers included were cardiovascular ICUs.

Dr Furnary. I am going to respond really quickly. First, there were no patients undergoing CABG in that trial, or at least certainly fewer than 100. Second, the Gandhi trial only studied intraoperative glycemic control, and the postoperative control was the same between groups. It was a very bad study.

My next question, and I think I know your answer to this, is in light of the serious statistical issues I have raised—and they are serious—would you consider restating your conclusion and retitling your article? Because you actually compared moderate control with no control, not moderate to tight.

Dr Ailawadi. The moderate control was not compared with no control; it was a more liberal control. It was essentially what was being done for many years until data became available.

Dr Furnary. Right, so it is moderate versus liberal.

Dr Ailawadi. It was a physician-directed protocol that many believe was the best at the time.

Dr Furnary. Would you agree that your study does not compare moderate versus tight control?

Dr Ailawadi. I would agree that our reference group is the liberal control group, not the tight control group, because the latter cannot be a reference group with only 134 patients.

Dr Furnary. So you compared moderate control with your reference group but not moderate control with tight control?

Dr Ailawadi. And we compared tight control with the reference group as well.

Dr Furnary. Thank you. So, finally, last question. With tight control in Portland, our 3-day blood glucose average is 115 mg/dL and our diabetes-associated CABG mortality in the last 10 years among more than 2000 such patients is 0.9%, with an STS observed to expected ratio of 0.25, a quarter of the national average mortality. So why do you think that the STS-derived observed to expected ratios contained within your data, but not explicitly presented, of 13.6 for tight control, 2.3 for moderate, and 1.45 for no control, were all significantly greater than 1?

Dr Ailawadi. Well, there are many potential reasons. Obviously, we are in a different situation, being at a training center, than you are at your institution. And although I cannot address that as the sole reason, an overall CABG mortality of roughly 2% is pretty similar to what the literature shows and what the

STS shows. I know that there has been an issue to try to get it down to 1%, and perhaps this will help us to do that, but I do believe that tight control may not be necessary.

I would want to emphasize that glucose control is a necessary thing. The question is, how tight do we really need to be? And if there are worse mortalities and higher complications with a tight strategy, then these findings of our study will be borne out in future randomized studies. So this is not the be-all and end-all; I agree with that. I think that this is an interesting study. We were a bit surprised to see the findings, and I think it should lead to better questioning in the future.

Dr Furnary. Thanks. I am sorry to rain on your parade. I think there is another rainmaker over there.

Dr Harold L. Lazar *(Boston, Mass).* I just need to disclose that we do have research support from the Eli Lilly Company but own no stock in the company.

When I heard that Dr Furnary was going to discuss this presentation, I didn't think that I would have too much more to question or add, but I would like to ask a couple of questions. When we wrote the guidelines for the STS a couple of years ago, we stated that the optimal glucose range would be between 120 to 180 mg/dL, and we did so not really to endorse tight versus moderate but to make it easier for people to have at least some compliance. Subsequently, our own group has done a study in which we looked at moderate versus aggressive control in a prospective randomized fashion, comparing 90 to 120 mg/dL versus 120 to 180 mg/dL. And what we found was that the tighter control group had better control of inflammatory factors such as free fatty acids, but in reality when we looked at the clinical end points and all the major adverse cardiac and cerebrovascular events, there was absolutely no difference.

So my first question to you is, why do you think that tight glycemic control was detrimental? We have seen that it may not add any more—at least in the short term, we can't comment on the long term—but why should it be bad? And in answering this question, I would like to ask you to focus on these points. What was the lowest glucose level that was reached? Did you actually have a formal protocol that actually titrated the glucose to achieve a certain level? And how often did you measure glucose, and what did you do when you reached the level that was lower, let's say, than 80 mg/dL?

Dr Ailawadi. Excellent questions. So the first question is, why do we think this is bad? And, again, we don't have data on the number of hypoglycemic events, but that is certainly a concern. There has been a fair amount of literature on the effects of neuroglycopenia, and, many patients in our population were still in the ICU, some of them still intubated. Those are difficult to assess, at least clinically, and merely can be measured with a glucose measurement.

In terms of the lowest glucose level reached, we had patients whose serum mean glucose levels were basically were as low as about 85 to 90 mg/dL.

Did we have a formal protocol? Before 1999, it was a physician-directed protocol. It was not a protocol enforced by the institution. From 1999, on we adopted the Portland protocol, which has since been modified as STS guidelines have improved, and we follow the STS guidelines quite carefully.

Dr Robert Scott Kramer *(Portland, Me).* We need to interpret the evidence supporting tight glycemic control with regard to the context where execution of the protocol at the bedside is the key to success. Well-trained and well-supervised bedside nurses can make a significant difference in the safety of a tight glycemic control program. Some nurses can manage an algorithm-driven insulin drip with the skill of a pilot keeping an airplane flying straight and level. I suspect that the NICE-SUGAR trial may have had some problems with the execution of the protocol at the bedside, because its hypoglycemia rate was so high. The lesson from NICE-SUGAR is that hypoglycemia is dangerous. Drs Furnary and Van den Berghe and others have taught us that a tight glycemic control protocol executed well at the bedside improves outcomes.

Dr Ailawadi. I believe that we have taken glucose control very seriously at the University of Virginia since the Portland diabetic project was first published. We have a number of people who are very interested in this, endocrinologists, nursing staff, and administrators, and our university is taking a very aggressive system-wide hospital approach. So I do believe that we feel very strongly that this is an important thing that we have undertaken.

Finally, in response to the question about how often we measure, in the past it had been a minimum of 12 measurements during a 24-hour period. That has now increased to a minimum of 18 measurements during a 24-hour period.

Dr Lazar. I am anxious to add just a follow-up to that. I think that the lack of a proper controlled regimen and not following these patients on an hourly basis and making adjustments may be contributory to some of the effects, because that is where people who have noted problems with tight glycemic control in surgical patients have gotten into trouble.

I guess my second question is, as we know, tight glycemic control is not only important in the first 24 hours but is important after the first 24 hours and before the patient goes home. So what protocols did you have in effect to look at the effect of glycemic control once the patient has left the ICU?

Dr Ailawadi. Essentially our strategy is when patients are receiving insulin infusions, we do get hourly blood glucose levels. When patients get out of the ICU from postoperative day 1 to 3, they are transitioned gradually to a sliding scale and the insulin infusion is turned off. This is all by protocol.